# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 020623

## STATISTICAL REVIEW(S)

Johnson

# STATISTICAL REVIEW AND EVALUATION --- NDA

Date: JUN 19 1996

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**NDA #**: 20-623

**Applicant**: Hoechst Marion Roussel, Inc

**Name of Drug**: Anzemet (Dolasetron mesylate) Tablet

**Indication**: Prevention of Postoperative Nausea and Vomiting

**Documents Reviewed**: Amendment dated May 21, 1996

**Medical Reviewer**: This review has been discussed with the medical Officer, Huqo Gallo-Torres, M.D., Ph.D.

## A. Background

The sponsor submitted this amendment to correct the evaluation of "complete response with no nausea" and "no nausea" that was reported in original NDA 20-623 submission dated September 28, 1995 for Protocol AN-PO-0292. The Protocol AN-PO-0292 was one of two adequate and well controlled trials that support the prevention of postoperative nausea and vomiting using dolasetron mesylate tablet.

In response to a finding by Mr. A. Keller, Investigator, Denver Federal Center, nausea data from this study were re-analyzed in a method consistent with data collection.

For the analysis of "no nausea" presented in the Integrated Summary of Efficacy (ISE) in the original NDA submission for dolasetron mesylate in the prevention of postoperative nausea and vomiting, "no nausea" was defined as a (maximum postdose) VAS score < 5 mm. Given the collection methodology actually employed, the incidence of "no nausea" presented for this study in the ISE is potentially an overestimate across all treatment groups. Similarly, there is a potential for the incidence of "complete response with no nausea" to have been overestimated.

The report amendment re-analyzes secondary efficacy parameters (complete response with no nausea and no nausea) using the discrete data points of "no nausea" that were collected during this trial.

B. **Sponsor's Response**

In this study, the severity of patient nausea was assessed using 200 mm VAS instead of 100 mm VAS in Study 095. Patients were to complete nausea VAS evaluations at baseline, end of recovery room stay, hour 8 and hour 24. Per protocol, patients were to complete a VAS evaluation at all scheduled timepoints, regardless of the presence or absence of nausea. However instructions to the sites (and on page 15 of the case report form), led to a discrepancy between the protocol and the case report form. Per these instructions, patients were to complete a VAS evaluation only if they answered "yes" to a verbal query about nausea in the time period preceding the scheduled evaluation. For patients responding "no", a nausea VAS score of 0 mm was imputed in the database; for patients responding "yes," the VAS score marked by the patient was entered.

A review of the case report form tabulations shows all patients reponing "yes" to nausea on a given evaluation to have corresponding nausea VAS score > 0 mm, when the evaluation was performed. In addition, some patients who initially responded "no" to the verbal query about nausea (recorded on the case report form), reported "yes" to the ward nurse, who entered "nausea" on the patient chart. When, at a later date, the sponsor clinical research associate requested a change to the case report form (CRF) so that it agreed with the medical chart, the CRF entry became nausea "yes" with no VAS score. These missing score were entered into the database as ".0". The missing VAS scores led to these evaluations being omitted from the determination of "no nausea" presented in the NDA submissions. These omissions resulted in the misclassification of complete response with no nausea for 5 out of the 373 patients who received study drug and underwent surgery.

This sponsor's amendment provides corrections for these omissions.

**1. Sponsor's Results of Re-analysis of Complete Response with No Nausea**

The summary of sponsor's results of re-analysis of complete response with no nausea is given below.

**Sponsor's Re-analysis of Complete Response with No Nausea**

**Protocol AN-PO-0292**
**Complete Response with No Nausea by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | P*-value vs placebo | P*-value vs Dola 25 | P*-value vs Dola 50 | P*-value vs Dola 100 |
|---|---|---|---|---|---|
| Placebo | 10/75 (13%) | | | | |
| Dola 25 | 21/75 (28%) | 0.0300 | | | |
| Dola 50 | 20/74 (27%) | 0.0354 | 0.9515 | | |
| Dola 100 | 29/74 (39%) | 0.0005 | 0.1314 | 0.1184 | |
| Dola 200 | 25/75 (33%) | 0.0043 | 0.4440 | 0.4110 | 0.4510 |

p=0.0013 for linear trend
No nausea is defined as a response of "no" to all postdose nausea evaluations.
P-value is calculated from a contrast of the parameter estimates
for dose obtained from a logistic regression model predicting complete
response with no nausea with dose and investigator as explanatory variables.
Compiled from Table 21, page 6 and Revised S8-V1.272-P109 in the Amendment

Contrary to the sponsor's finding in the NDA submission, in this re-analysis of comparisons of each dose to placebo of the proportion of complete responders with no nausea showed a statistically significant difference in the 25 mg dose group.

C. **Reviewer's Evaluation**

The five patients who were misclassified as complete responder with no nausea were: one each in placebo, dolasetron 50 mg, and dolasetron 100 mg groups; and two in dolasetron 200 mg group.

There was no disproportionate misclassification among treatment group. The corrections which occurred in only one to two patients in each group resulted the minimum impact of the efficacy results in favor of dolasetron 100 mg against the sponsor's proposed dose of 50 mg.

This reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The summary of results is given below.

**Reviewer's Alternative Analysis of Complete Response with No Nausea using Corrected Data**

**Protocol AN-PO-0292**
**Complete Response with No Nausea by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | P*-value vs placebo | P*-value vs Dola 25 | P*-value vs Dola 50 | P*-value vs Dola 100 |
|---|---|---|---|---|---|
| Placebo | 10/75 (13%) | | | | |
| Dola 25 | 21/75 (28%) | 0.043 | | | |
| Dola 50 | 20/74 (27%) | 0.065 | 1.000 | | |
| Dola 100 | 29/74 (39%) | <0.001 | 0.168 | 0.119 | |
| Dola 200 | 25/75 (33%) | 0.006 | 0.596 | 0.476 | 0.498 |

No nausea is defined as a response of "no" to all postdose nausea evaluations.
P-values were obtained by this reviewer using Fisher's exact test.
Compiled from Table 21 in the Amendment

Comparing the results given above with the one given in Table 3 in the Statistical Review and Evaluation dated May 20, 1996 using data from NDA submission (see below), there were no changes in terms of significance for dolasetron 100 mg and 200 mg groups. But, the p-value for dolasetron 25 mg group was changed from 0.072 to 0.043 (from nonsignificance to significance); the p-value for dolasetron 50 mg group was changed from 0.048 to 0.065 (from significance to nonsignificance).

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**Reviewer's Alternative Analysis of Complete Response with No Nausea using NDA Data**

**Protocol AN-PO-0292**
**Complete Response with No Nausea by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | P*-value vs placebo | P*-value vs Dola 25 | P*-value vs Dola 50 | P*-value vs Dola 100 |
|---|---|---|---|---|---|
| Placebo | 11/75 (15%) | | | | |
| Dola 25 | 21/75 (28%) | 0.072 | | | |
| Dola 50 | 21/74 (28%) | 0.048 | 1.000 | | |
| Dola 100 | 30/74 (41%) | <0.001 | 0.122 | 0.166 | |
| Dola 200 | 27/75 (36%) | 0.004 | 0.382 | 0.382 | 0.615 |

No nausea is defined postdose maximum VAS score < 5 mm.
P-values were obtained by this reviewer using Fisher's exact test.
Compiled from Table 21 in the Amendment

For lower doses (25 mg and 50 mg), with a few corrections (one patient in placebo and one patient in dolasetron 50 mg) made, this correction resulted a change of nonsignificance to significance for dolasetron 25 mg group and a change of significance to nonsignificance for dolasetron 50 mg group in the reviewer's alternative analyses. This casts doubt of the robustness of the results.

For higher doses (100 mg and 200), significance was observed both in the this reviewer's alternative analysis of data with corrections and NDA data. The results for these doses were robust.

D. **Overall Summary and Recommendation**

The five patients who were misclassified as complete responder with no nausea were: one each in placebo, dolasetron 50 mg, and dolasetron 100 mg groups; and two in the dolasetron 200 mg group. There was no disproportionate misclassification among treatment group.

For lower doses (25 mg and 50 mg), with a few corrections (one

patient in placebo and one patient in dolasetron 50 mg) made, this correction resulted a change of nonsignificance to significance for dolasetron 25 group and a change of significance to nonsignificance for 50 mg group in this reviewer's alternative analyses. This casts doubt of the robustness of the results.

For higher doses (100 mg and 200 mg), significance was observed in the sponsor's re-analysis and this reviewer's alternative analysis of data with corrections and in the sponsor's analysis and this reviewer's alternative analysis of NDA data. The results for these doses were robust.

These corrections do not have any impact on the recommendation of 100 mg for prevention of postoperative nausea and vomiting stated in this reviewer's NDA Statistical Review and Evaluation.

E. **Comments to be conveyed to the Sponsor**

The contents of Section D may be conveyed to the sponsor.

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/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 6 pages of text and 0 page of table.

Concur: Dr. Huque /S/ 6/19/96
Dr. Smith /S/ 6/19/96

cc:
Archival NDA 20-623
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Liscook
HFD-720
HFD-720/Chron. Copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/73088/mcf/06/17/96

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# STATISTICAL REVIEW AND EVALUATION --- NDA

**Date:** MAY 20 1996


**NDA #** 20-623

**Applicant:** Hoechst Marion Roussel, Inc.

**Name of Drug:** Anzemet (Dolasetron mesylate) Tablet

**Indication:** Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy, Including Initial and Repeat Courses.

**Documents Reviewed:** NDA vol. 1.1-1.3, 1.175, 1.222-1.279, 588-591, 682 Dated September 28, 1995.

**Medical Reviewer:** This review has been discussed with the medical officer, Hugo Gallo-Torres, M.D., Ph.D.

## A. Background

Dolasetron mesylate is a selective serotonin type 3 ($5\text{-}HT_3$) receptor antagonist under development by the sponsor for the prevention of nausea and vomiting due to chemotherapy and surgery.

In the current NDA, the sponsor seeks approval of oral dolasetron mesylate in two primary indications: for prevention of CCNV (cancer chemotherapy induced nausea and vomiting), and for prevention of PONV (postoperative nausea and vomiting).

This review addresses only the prevention of CCNV.

## B. CCNV Indication

The sponsor has submitted three clinical trials (MCPR0048, MCPR0043, 73147-2-S-087) in support of the proposed claims: for prevention of CCNV.

These studies were not limited to chemotherapy naive patients.

Doses of 25, 50, 100 and 200 mg were chosen for these trial from results of iv trials.

The primary efficacy variable was "complete response," defined as 0 emetic episodes and no rescue medication during the 24 study period. The definition of "emetic episode" in the three adequate and well-controlled trials (MCPR0048, MCPR0043, 73147-2-S-087) for oral dolasetron mesylate was: a single episode of vomiting or any number of retches (nonproductive emesis) with a unique 5-minute period.

Secondary efficacy variables were: "complete-or-major response": (0-2 emetic episodes and no rescue medication during the 24-hour study period), time to first emetic episode or rescue medication, patients' self-report of nausea and overall satisfaction with antiemetic therapy, and complete response with no nausea.

The latter, added as requested by FDA, was a more stringent efficacy measure derived by superimposing a nausea criterion on patients who met criteria for "complete response." Nausea was evaluated by asking patients to mark a 100 mm visual analog scale (VAS) labeled "No nausea" at 0 mm and "Nausea at bad as it can be" at 100 mm. The mark was based upon the severity of nausea experienced over the 24-hour study period. Patients whose nausea VAS was marked <5mm from the end labeled "No nausea," and who did not vomit or require rescue medication were included as patient with complete response with no nausea.

C. **Study MCPR0048**

1. **Description of Study**

This was a four-arm double-blind, randomized multicenter study, conducted at 32 sites in the U.S., of oral dolasetron mesylate with intravenous a cyclophosphamide and/or doxorubicin-containing chemotherapy. The primary emetogenic challenge was cyclophosphamide and/or doxorubicin.

Patients were randomly assigned to one of four dolasetron mesylate doses: 25 mg, 50 mg, 100 mg, or 200 mg. A single oral dose of study medication was taken 30 minutes prior to the start of iv cyclophosphamide or iv doxorubicin-containing chemotherapy. No other medication with antiemetic activity were to be allowed during the 24 hours prior to or the 24 hours after the initiation of the primary emetic.

Cyclophophamide and doxorubicin were administered during the study in the following doses: cyclophosphamide 500-1200 mg/m$^2$, doxorubicin 25-75 mg/m$^2$ in combination chemotherapy, or doxorubicin>=40 mg/m$^2$ as a single agent. The primary emetic challenge would be infused over no longer than 2 hours.

Patients with a previous chemotherapy history were admitted provided it did not include cyclophosphamide or doxorubicin, and the patient had not vomited with any prior chemotherapy.

If patient experienced at least three emetic episodes during the 24-hour evaluation period after the start of chemotherapy or requested alternative antiemetic therapy, the investigator might initiate escape medication.

The primary efficacy endpoint was complete response (0 emetic episode, no rescue medication, and monitored for emesis at least 23.5 hours). Patients not monitored for emesis at least 23.5 hours were considered as treatment failures.

The secondary efficacy endpoints were complete-plus-major response (0-2 emetic episode), time to first emetic episode, severity of nausea measured by visual analogue scales (VAS), patient satisfaction with antiemetic therapy measured by a VAS, and time to rescue therapy.

The primary analysis was to be based on a logistic regression model using treatment and investigator as independent predictors.

Time to first emetic episode and time to escape medication were to be analyzed using survival techniques. For time to first emetic episode, patients who did not experience emesis during the follow-up or patients who received escape medication with no emetic episode were to be treated as censored values.

The Cox regression model was to be used to analyze the dose trend of dolasetron mesylate with adjusting for other covariates.

Sample size determination is based on establishing a linear trend in complete response with dose using a logistic regression. Power calculations for various alternatives are given in table below. These calculations were based on a 2-sided 0.05 significance test and 75 patients in each dose group. Any observed complete

response which increased with dose at a rate which amounts to a least a 25% increase would have at least 90% power, provided the 25 mg group has response rate between 25% and 35%. Any dose response rate which is lower than a 20% increase would be detected with approximately less than 75% power with these same assumptions.

**Percent Complete Responses Postulated by Alternative Hypotheses**

| 25 mg | 50 mg | 100 mg | 200 mg | Power |
|---|---|---|---|---|
| 25% | 33% | 42% | 51% | 93% |
| 25% | 31% | 38% | 45% | 77% |
| 35% | 43% | 52% | 61% | 91% |
| 35% | 41% | 48% | 55% | 73% |

2. **Sponsor's Analysis**

A total of 320 patients were enrolled and were conducted in 32 investigators. Seventy-nine (79) received dolasetron mesylate 25 mg, 83 received dolasetron mesylate 50 mg, 80 received dolasetron mesylate 100 mg, and 78 received dolasetron mesylate 200 mg.

All randomized patients received study drug, and were included in the intent-to-treat efficacy analysis. All randomized patients who did not have protocol deviation were included in efficacy evaluable analysis.

Patient MCST0319-0019 who received 25 mg dolasetron mesylate did not receive chemotherapy because she refused her chemotherapy treatment. Therefore 319 patients received study, and underwent their first course of chemotherapy. These 319 patients were included in the intent-to-treat analysis. Seven patients (1 in 25 mg, 2 in 50 mg, 1 in 100 mg, and 3 in 200 mg dose group) were considered to have major protocol violations and were excluded from the evaluable analysis.

Logistic regression with a test for linear trend in the proportion of complete responders with dose, controlling for

investigator as a main effect, was the primary test for efficacy. The presence of an interaction between investigator and a linear dose response was examined using logistic regress and the Rao scores (residual chi-square) test.

As requested by FDA, a further secondary efficacy endpoint was added, complete response with no nausea.

Several efficacy endpoints were considered in this study. However, one of these endpoints and a corresponding test (complete response, test for linear trend with dose) were identified a priori as the primary test for efficacy in both the protocol and the statistical analysis plan. All other analyses and endpoints are considered secondary to the primary analysis. Thus, no multiple comparison adjustments were made.

**Pooling of Sites**

In the analyses, all "small" sites were be grouped together into pooled site(s). A site was considered to have insufficient data and to be a candidate for pooling if it failed to have at least five successes (complete responders) and five failures (major responders or treatment failures). Insufficient-data sites were be ordered on the basis of number of patients. Beginning with the smallest of these sites, sites were be added sequentially to a pooled site, until the pooled site met both of the above criteria. Subsequent insufficient-data sites would be entered into another pooled site, until the new pooled site meets the criteria. This process would continue until the largest of the insufficient-data sites had been pooled together.

Twenty-three sites were grouped into six pooled sites to satisfy asymptotic considerations for main effects logistic regression and minimum information criteria for the secondary Mantel-Haenszel test. The following pooled sites were created: MCST0312, 0316, 0321, 0324, 0331, 0379, and 0383; 0380, 0386, 0388, 0390, and 0391; 0322, 0332, 0382, and 0385; 0326 and 0333; 0328 and 0353; 0315, 0334, and 0335.

## 2.1 Treatment Group Comparability

The summary of results of comparability of treatment groups at

baseline is given in Table 1.

There were no statistically significant differences among the four dose groups with respect to gender, race, age, weight, height, Kamofsky performance status, history of heavy alcohol use, and site of primary neoplasm.

There was no statistically significant imbalances among dose groups in primary chemotherapy, cyclophosphamide and doxorubicin use (single agent or both agents), duration of primary chemotherapy infusion, and interval between study drug administration and primary chemotherapy infusion.

However, there were statistically significant imbalances among the four dose groups in cyclophosphamide dose ($p=0.0321$) and doxorubicin dose ($p=0.0032$). The 200 mg dose group had the lowest mean doses for both agents. For cyclophosphamide, the mean doses were 641.5 $mg/m^2$, 623.8 $mg/m^2$, 606.7 $mg/m^2$, and 580.4 $mg/m^2$ for the 25 mg, 50 mg, 100 mg, and 200 mg dose groups, respectively. For doxorubicin, the mean doses were 45.1 $mg/m^2$, 45.7 $mg/m^2$, 42.6 $mg/m^2$, and 40.8 $mg/m^2$ for the 25 mg, 50 mg, 100 mg, and 200 mg dose groups, respectively.

There were statistically significant imbalances among the four dose groups in escape medications. The incidences of the use of prochlorperazine ($p=0.021$) and lorazepam ($p=0.030$) were higher in the lower dolasetron mesylate dose groups.

## 2.2 **Sponsor's Analysis of Primary Efficacy Parameter**

The primary efficacy parameter is complete response. Complete response was achieved for a patient when he or she experienced no emetic episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of results of sponsor's analysis of complete response is given below.

**Protocol MCPR0048**
**Complete Response by Dose**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs 25 mg | p*-value vs 50 mg | p*-value vs 100 mg |
|---|---|---|---|---|
| 25 | 24/78 (31%) | | | |
| 50 | 34/83 (41%) | 0.1801 | | |
| 100 | 49/80 (61%) | 0.0002 | 0.0097 | |
| 200 | 46/78 (59%) | 0.0004 | 0.0209 | 0.7921 |

p<0.0001 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

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There was a significant linear trend in complete response rates with dolasetron mesylate doses with the highest complete response rate achieved with the 100 mg dose. The 100 mg and 200 mg doses were not significantly different, and both were significantly more effective than the 25 mg and 50 mg doses. There was no statistically significant difference between the 25 mg and 50 mg dose groups, nor between the 100 mg and 200 mg dose groups.

### 2.3 Sponsor's Analysis of Secondary Efficacy Parameters

The secondary efficacy parameters are complete-plus-major response, time to first emetic episode or escape medication, nausea, and FDA requested complete response with no nausea.

#### 2.3.1 Complete-Plus-Major Response

Major response was achieved for a patient when he or she experienced one or two episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of results of sponsor's analysis of complete-plus-

major response is given below.

**Protocol MCPR0048**
**Complete-Plus-Major Response by Dose**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs 25 mg | p*-value vs 50 mg | p*-value vs 100 mg |
|---|---|---|---|---|
| 25 | 28/78 (36%) | | | |
| 50 | 43/83 (52%) | 0.0420 | | |
| 100 | 52/80 (65%) | 0.0003 | 0.0791 | |
| 200 | 56/78 (72%) | <0.0001 | 0.0066 | 0.3154 |

p<0.0001 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete-plus-major response with dose and investigator as explanatory variables.

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The test for linear trend in the proportion of complete-plus-major responders with dose was statistically significant. There were statistically significant differences among the four dose groups. The 50 mg, 100 mg, and 200 mg dose groups were significantly different from the 25 mg dose group. In addition, the 200 mg dose group was significantly different from the 50 mg dose group. There was no statistically significant difference between the 50 mg and 100 mg dose groups, nor between the 100 mg and 200 mg dose groups.

### 2.3.2 Complete Response with No Nausea

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent, and had an hour 24 nausea VAS less than 5 mm.

The summary of results of analysis of complete response with no nausea is given below.

**Protocol MCPR0048**
**Complete Response with No Nausea by Dose**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs 25 mg | p*-value vs 50 mg | p*-value vs 100 mg |
|---|---|---|---|---|
| 25 | 16/78 (21%) | | | |
| 50 | 22/83 (27%) | 0.3665 | | |
| 100 | 30/80 (38%) | 0.0181 | 0.1244 | |
| 200 | 31/78 (40%) | 0.0079 | 0.0645 | 0.7407 |

p=0.0028 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with no nausea with dose and investigator as explanatory variables.

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The test for linear trend with dose in the proportion of complete responders with no nausea was statistically significant. There were statistically significant differences among the four dose groups. The 100 mg and 200 mg dose groups were significant different from the 25 mg dose group. There was no statistically significant difference between the 25 mg and 50 mg dose groups, nor between the 50 mg and 100 mg doses, nor between the 50 mg and 200 mg doses, nor between the 100 mg and 200 mg dose groups.

## 3. Reviewer's Evaluation and Comments

### 3.1 Dose Response

The dose response was significant with a small p-value for complete response, complete-plus-major response, and complete response with no nausea.

### 3.2 Sponsor's Sample Size Determination

Sponsor's sample size determination is based on establishing a linear trend in complete response with dose using a logistic regression. The sample size might be insufficient to detect the dose differences in a pairwise manner. The sample size might not be large enough to detect the differences between 100 mg and 200

mg.

### 3.3 Dose of Cyclophosphamide and Doxorubicin Chemotherapy

In this study population, 301 patients received cyclophosphamide; the doses ranged from with a mean of 613.9 mg/m$^2$. Of these, three patients (MCST0323-0011, 0381-0008, and 0381-0012) received low-dose oral cyclophosphamide (115.5 mg/m$^2$, 31.0 mg/m$^2$, and 98.9 mg/m$^2$, respectively). Two hundred eleven (211) patients received doxorubicin in doses ranging from 15.9 to 75.1 mg/m$^2$, with a mean of 43.6 mg/m$^2$. Of the patients receiving doxorubicin, 35 patients (all patients at site MCST0327) received continuous infusion doxorubicin in doses ranging which was much less than the mean of 43.6 mg/m$^2$.

### 3.4 Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

The sponsor used logistic regression method to test the linear trend. The logistic regression method is a model based approach. It has been used mainly in the explorative analysis. For confirmatory analysis, the design based approaches, e.g. Mantel-Haenzel, Fisher's exact test might be more appropriate.

This reviewer performed an alternative analysis of complete response using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 2.

As seen from Table 2, the results by Fisher's exact test are similar to those given the sponsor using logistic regression mehtod in terms of significance.

### 3.5 Reviewer's Comments on Sponsor's Results for the Secondary Efficacy

The FDA required efficacy endpoint of complete response with no nausea is more stringent than complete response specified in the protocol.

This reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given below.

**Protocol MCPR0048**
**Complete Response with No Nausea by Dose**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs 25 mg | p*-value vs 50 mg | p*-value vs 100 mg |
|---|---|---|---|---|
| 25 | 16/78 (21%) | | | |
| 50 | 22/83 (27%) | 0.458 | | |
| 100 | 30/80 (38%) | 0.023 | 0.178 | |
| 200 | 31/78 (40%) | 0.014 | 0.014 | 0.870 |

P* is obtained by Fisher's exact test.

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Contrary to sponsor's finding, in terms of the proportion of complete responders with no nausea, the 200 mg dose group was significantly different from the 50 mg dose group.

D. **Study MCPR0043**

1. **Description of Study**

This was a four-arm, double-blind, randomized multicenter study, conducted in the U.S., of oral dolasetron mesylate in patients receiving moderately emetogenic chemotherapy. The emetogenic challenge was carboplatin mg/m² or low-dose cisplatin mg/m².

The design of this study was similar to that of study MCPR0048.

Patients with previous chemotherapy were eligible for admission only if the previous chemotherapy had not included the primary emetogenic stimulus in the dolasetron mesylate study, and if they had not experienced significant nausea and vomiting.

Patient could receive either carboplatin or cisplatin, but not both.

2. **Sponsor's Analysis**

A total of 307 patients, 165 male and 142 female, were enrolled and were conducted in 32 investigators in this study. Seventy-six (76) received dolasetron mesylate 25 mg, 80 received

dolasetron mesylate 50 mg, 71 received dolasetron mesylate 100 mg, and 80 received dolasetron mesylate 200 mg.

Twenty-one (31) patients (8 in 25 mg, 9 in 50 mg, 5 in 100 mg, and 9 in 200 mg dose groups) were considered to have major protocol violations. These patients were excluded from the efficacy evaluable patient analysis.

Five patients were excluded from the efficacy evaluable analysis due to receiving doses of carboplatin considered to be too low to constitute a moderate emetogenic stimulus (<247.5 mg/m$^2$).

Six patients were excluded from the efficacy evaluable analysis due to receiving doses of carboplatin or cisplatin considered to be too high to constitute a moderate emetogenic stimulus (>440 mg/m$^2$ carboplatin or >55 mg/m$^2$ cisplatin).

Twenty-four sites were grouped into 8 pooled sites to satisfy asymptotic considerations for main effects logistic regression and minimum information criteria for the secondary Mantel-Haenszel test. The following pooled sites were created: MCST0152, 0154, 0157, 0175, 0186, and 0190; 0153, 0155, 0179 and 0188; 0160, 0163, 0184, and 0185; 0169 and 0394; 0183 and 0189; 0167, and 0173; 0176 and 0178; 0171 and 0174.

## 2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 3.

There were no statistically significant differences among the four dose groups with respect to gender, race, age, weight, height, Kamofsky performance status, and history of heavy alcohol use.

There were no statistically significant imbalances among dose groups in previous cancer treatment history, previous medications, use of concomitant chemotherapies, concomitant medications, primary chemotherapy, chemotherapy doses, duration of primary chemotherapy infusion, and interval between study drug administration and primary chemotherapy infusion.

There was statistically significant imbalance among the dose

groups in the incidence of the use of steroids (p=0.0336): the 100 mg dose group had a higher incidence than the other three dose groups.

There were statistically significant imbalances among dose groups in the use of escape medications. The incidence of the use of lorazepam (p=0.011) was higher in the 25 mg dose group.

## 2.2 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy parameter is complete response. Complete response was achieved for a patient when he or she experienced no emetic episodes, received no escape medication, and was monitored for at least 23.5 hours after initiation of the chemotherapy.

The summary of results of sponsor's analysis of complete response is given below.

**Protocol MCPR0043**
**Complete Response by Dose**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs 25 mg | p*-value vs 50 mg | p*-value vs 100 mg |
|---|---|---|---|---|
| 25 | 34/76 (45%) | | | |
| 50 | 57/80 (71%) | 0.0006 | | |
| 100 | 52/71 (73%) | 0.0005 | 0.8289 | |
| 200 | 66/80 (83%) | <0.0001 | 0.0907 | 0.1527 |

p<0.0001 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

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There was a highly significant linear trend in complete response rates with increasing doses of dolasetron mesylate. There were statistically significant differences among the four dose groups. The 50 mg, 100 mg, and 200 mg dose groups were significantly different from the 25 mg dose. With little power for detecting dose differences, there were no statistically significant

differences among the 50 mg, 100 mg, and 200 mg dose groups.

The results of the secondary analyses of primary endpoint were consistent with the primary analysis. The Mantel-Haenszel test for non-zero correlation between dose and complete response was statistically significant.

### 2.3 **Sponsor's Analysis of Secondary Efficacy Parameters**

The secondary efficacy parameters are complete-plus-major response, time to first emetic episode or escape medication, nausea, and FDA requested complete response with no nausea.

#### 2.3.1 **Complete-Plus-Major Response**

Major response was achieved for a patient when he or she experienced one or two episodes, received no escape medication, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of results of sponsor's analysis of complete-plus-major response is given below.

**Protocol MCPR0043**
**Complete-Plus-Major Response by Dose**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs 25 mg | p*-value vs 50 mg | p*-value vs 100 mg |
|---|---|---|---|---|
| 25 | 42/76 (55%) | | | |
| 50 | 62/80 (78%) | 0.0030 | | |
| 100 | 55/71 (78%) | 0.0048 | 0.9737 | |
| 200 | 70/80 (88%) | <0.0001 | 0.1088 | 0.1115 |

p=0.0001 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete-plus-major response with dose and investigator as explanatory variables.

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The test for linear trend in the proportion of complete-plus-

major responders with dose was statistically significant. There were statistically significant differences among the four dose groups. The 50 mg, 100 mg, and 200 mg dose groups were significantly different from the 25 mg dose group. However, there was no statistically significant difference among the 50 mg, 100 mg, and 200 mg dose groups.

### 2.3.2 Complete Response with No Nausea

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent, and had an hour 24 nausea VAS less than 5 mm.

**Protocol MCPR0043**
**Complete Response with No Nausea by Dose**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs 25 mg | p*-value vs 50 mg | p*-value vs 100 mg |
|---|---|---|---|---|
| 25 | 25/76 (33%) | | | |
| 50 | 39/80 (49%) | 0.0462 | | |
| 100 | 44/71 (62%) | 0.0004 | 0.0834 | |
| 200 | 56/80 (70%) | <0.0001 | 0.0058 | 0.3331 |

p<0.0001 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with no nausea with dose and investigator as explanatory variables.

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The test for linear trend with dose in the proportion of complete responders with no nausea was statistically significant. There were statistically significant differences among the four dose groups. The 50 mg, 100 mg, and 200 mg dose groups were significantly different from the 25 mg dose group. The 200 mg dose group was significantly different from the 50 mg dose group.

## 3. Reviewer's Evaluation and Comments

### 3.1 Dose Response

The dose response was significant with a small p-value with the highest rate achieved with the 200 mg for complete response, complete-plus-major response, and complete response with no nausea.

### 3.2 Sponsor's Sample Size Determination

Sponsor's sample size determination is based on establishing a linear trend in complete response with dose using a logistic regression. The sample size might be insufficient to detect the dose differences in a pairwise manner. The sample size might not be large enough to detect the differences between 100 mg and 200 mg.

### 3.3 Imbalance at Baseline

There were slightly imbalance in cisplatin dose, previous history radiotherapy, concomitant use of steroids among dose groups (p=0.0720, 0.0794, 0.0336, respectively).

### 3.4. Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

This reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 4.

As seen from Table 4, the results by Fisher's exact test are similar to those given the sponsor using logistic regression method in terms of significance.

### 3.3 Reviewer's Comments on Sponsor's Results for the Secondary Efficacy

For complete-plus-major response and complete response with no nausea, this reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 5.

As seen from Table 5, the results by Fisher's exact test are similar to those given by the sponsor using logistic regression method in terms of significance.

The sponsor also performed analysis of no nausea (VAS scores < 5mm) using the logistic regression model with dose and investigator as explanatory variables. The pairwise comparison showed that without adjustment for multiple comparison, the 100 mg group was not significantly different from the 50 mg group, but the 200 mg group was significantly different than 50 mg group (p=0.0289).

In this study, due to insufficient sample size there was no enough power to detect the difference between 100 mg and 200 mg groups. But, there was a numerical difference of about 10% in favor of 200 mg group in complete response, complete-plus-major response and complete response with no nausea. So the 200 mg might be the optimal effective dose.

E. **Study 73147-2-S-087**

1. **Description of Study**

This was a five-arm, double-blind, randomized multicenter study, conducted in Europe, of the antiemetic efficacy of single oral doses of dolasetron mesylate 50, 100, 200 or 300 mg or ondansetron in cancer patients receiving moderately emetogenic chemotherapy. The first amendment subtracted a 300 mg dose of dolasetron mesylate from the study design. The second amendment added a 25 mg dose of dolasetron mesylate to the study design.

Patients enrolling in this trial were stratified by gender and previous exposure to chemotherapy, and randomly assigned to treatment with 25 mg, 50 mg, 100 mg or 200 mg dolasetron mesylate or ondansetron.

Each patient received in a blinded manner one of four doses of dolasetron mesylate 1 hour before the start of chemotherapy or a standard ondansetron regimen of 8 mg orally 1.5 hours before and 6.5, 14.5 and 22.5 hours (32 mg total dose) after the start of the chemotherapy. The fourth dose (22.5 hour) of ondansetron was deleted in four Italian centers per amendment.

- A variety of primary chemotherapies were permitted, including carboplatin, low dose cisplatin (>=20 mg/m$^2$ and <=40 mg/m$^2$), cyclophosphamide and anthracyclines.

  It included non-naive patients, even if they had vomited after their previous chemotherapy.

  Efficacy parameters was to be evaluated in the 24 h following the start of chemotherapy.

  Other drugs with anti-emetic efficacy may be used as escape/rescue therapy if:

  a). More than 2 emetic episodes (>2) occur during the 24 h following the start of chemotherapy.

  b). The patient demands alternative anti-emetic therapy.

  Nausea would be assessed by patients and investigators. Patients would assess nausea with a visual analogue scales (VAS). Patients would make assessment before the first 2 study drug administration (1.5 and 1 h before the start of chemotherapy), just before and 24 h after the start of the chemotherapy. The assessment at 24 h would be of nausea at worst during the 24 h study period. Investigators would make an assessment of nausea based on a simple 4-point scale (none, mild, moderate, severe). The assessment would record the severity of nausea at worst in the periods 0-8 and 8-24 h after the start of chemotherapy.

  The number of emetic episodes would be recorded within each hour from 0-24 h after the start of chemotherapy.

  The primary efficacy variable was the proportion of complete responders (0 emetic episodes) in the 24 h period after chemotherapy. Patients who withdraw due to adverse events, lack of effect (>2 emetic episodes during the 24 h period) or use escape medication due to patient demand would be considered as treatment failure.

  All dose groups would be compared with respect to the proportion of complete responders (no emetic episode), and major responders (1-2 emetic episodes), and the proportion of failures during the 24 h study period. The times to the first emetic episode, onset

of nausea and to the introduction of escape medication during the same period would be evaluated using survival analysis methodology.

The sample size was determined by assuming percentage of complete responders to be 50% and 70% for ondansetron and dolasetron mesylate, respectively with alpha=0.05 and 80% power. This sample determination yielded a sample size of 75 patients per arm. A total of 375 patient would be recruited.

2. **Sponsor's Analysis**

A total of 399 patients were randomized to treatment and received study drug. A total of 316 patients received dolasetron mesylate: of these, 80 received 25 mg, 80 received 50 mg, 76 received 100 mg, and 80 received 200 mg once daily. Eighty-three (83) patients received oral ondansetron, 62 received ondansetron 8 mg x 4 doses, and 21 received ondansetron 8 mg x 3 doses.

All randomized patients received study drug, and were included in the Intent-to-Treat efficacy dataset, except any patients who did not receive chemotherapy. An efficacy evaluable dataset was constructed by removing those patients having protocol deviation that might impact the occurrence or severity of nausea and vomiting.

Twenty-five patients (6 in ondasetron, 9 in 25 mg dolasetron, 8 in 50 mg dolasetron, 1 in 100 mg dolasetron, and 1 in 200 mg dolasetron)were considered to have major protocol violations. These patients were excluded from the efficacy evaluable dataset.

Fourteen sites were grouped into 4 pooled sites to satisfy asymptotic considerations for main effects logistic regression and minimum information criteria for the secondary Mantel-Haenszel test. The following pooled investigators were created: 22, 29, 43, 44, and 49; 10, 26, 42, and 46; 5, 39, and 53; 38 and 40.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 6.

- There were no statistically significant differences among the five treatment groups with respect to gender, age, weight, height, and Karnofsky performance status.

There were no marked imbalances in previous and/or concurrent diseases, previous cancer treatment history, and previous medications among the five treatment groups

There were no statistically significant imbalances among treatment groups in primary chemotherapy, chemotherapy regimen, or chemotherapy doses.

There were no statistically significant imbalances among the five treatment groups in use of concomitant chemotherapies, concomitant medications, escape medications.

2.2 **Sponsor's Analysis of Primary Efficacy Parameter**

The primary efficacy endpoint was complete response. Complete response was achieved for a patient when he or she experienced no emetic episodes, received no escape medication, and was monitored for emesis for at least 23.5 hours after initiation of chemotherapy administration. Patients not monitored for at least 23.5 hours were considered treatment failures.

**Protocol 73147-2-S-087**
**Complete Response by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs Onda | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Onda | 60/83 (72%) | | | | |
| Dola 25 | 36/80 (45%) | 0.0003 | | | |
| Dola 50 | 39/79 (49%) | 0.0011 | 0.6584 | | |
| Dola 100 | 46/76 (61%) | 0.0640 | 0.0638 | 0.1613 | |
| Dola 200 | 61/80 (76%) | 0.5787 | <0.0001 | 0.0002 | 0.0184 |

p<0.0001 for linear trend in dolasetron mesylate dose.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with treatment, stratum, and investigator as explanatory variables.

There was a significant linear trend in complete response rates with dolasetron mesylate dose, with the highest complete response rate achieved with the 200 mg dose. This dose was significantly more effective than each of the three lower dolasetron mesylate doses and equivalent to the European approved oral multiple dose regimen of ondansetron (8 mg x 4 doses).

The complete response rate with dolasetron 200 mg is similar to that observed with the active comparator ondansetron.

The results of the secondary analyses of the primary endpoint were consistent with the primary analysis. The Mantel-Haenszel test for non-zero correlation between dolasetron mesylate dose and complete response was statistically significant.

2.3 **Sponsor's Analysis of Secondary Efficacy Parameters**

The secondary efficacy parameters are complete-plus-major response, time to first emetic episode or escape medication, nausea, and FDA requested complete response with no nausea.

2.3.1 **Complete-Plus-Major Response**

Major response was achieved for a patient when he or she experienced one or two episodes, received no escape medication, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of results of sponsor's analysis of complete-plus-major response is given below.

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**Protocol 73147-2-S-087**
**Complete-Plus-Major Response by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs Onda | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Onda | 65/83 (78%) | | | | |
| Dola 25 | 46/80 (58%) | 0.0007 | | | |
| Dola 50 | 47/79 (60%) | 0.0040 | 0.5477 | | |
| Dola 100 | 55/76 (72%) | 0.1499 | 0.0454 | 0.1591 | |
| Dola 200 | 68/80 (85%) | 0.3159 | <0.0001 | 0.0002 | 0.0188 |

p<0.0001 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with treatment, stratum, and investigator as explanatory variables.

The test for linear trend in the proportion of complete-plus-major responders with dolasetron mesylate dose was statistically significant ($p<0.001$).

There were statistically significant differences among the four dolasetron mesylate dose groups. The 200 mg dose group was significantly different from the 25 mg, 50 mg, and 100 mg dose group. The 100 mg dose group was significantly different from the 25 mg dose group. There was no statistically significant difference between the 25 mg dose and 50 mg dose groups, nor between the 50 mg and 100 mg dose groups.

There was no statistically significant difference between ondansetron and the dolasetron mesylate 200 mg, nor between ondansetron and the dolasetron mesylate 100 mg.

### 2.3.2 Complete Response with No Nausea

The most stringent test for efficacy was complete response with no nausea. Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, was monitored for at least 23.5 hours

- after initiation of the primary chemotherapy agent, and had an hour 24 nausea VAS less than 5 mm.

**Protocol 73147-2-S-087**
**Complete Response with No Nausea by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs Onda | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Onda | 41/83 (49%) | | | | |
| Dola 25 | 29/80 (36%) | 0.0303 | | | |
| Dola 50 | 26/79 (33%) | 0.0096 | 0.6577 | | |
| Dola 100 | 37/76 (49%) | 0.5814 | 0.1055 | 0.0426 | |
| Dola 200 | 51/80 (64%) | 0.1005 | 0.0002 | <0.0001 | 0.0323 |

p<0.0001 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with treatment, stratum, and investigator as explanatory variables.

The test for linear trend with dolasetron mesylate dose in the proportion of complete responders with no nausea was statistically significant. There were statistically significant differences among the four dose groups. The 200 mg dose group was significantly different from the 25 mg, 50 mg, and 100 mg dose groups. The 100 mg dose group was significantly different from the 50 mg dose group. There was no statistically significant difference between the 25 mg dose and 50 mg dose groups, nor between the 25 mg and 100 mg dose groups.

## 3. Reviewer's Evaluation and Comments

### 3.1 Reviewer's Comments

#### 3.1.1 Randomization

For some patients, more than one treatment were assigned and study drug given to the same patient (1 patient in Center NO. 4 and Center No 8). Some patients were assigned out of sequence (1

patient in Center No. 1, Center 4, Center 15, Center 26, and Center 29; 2 patients in Center No. 20; 3 patients in Center No. 21; 7 patients in Center 23). There was a serious problem of assigning patients out of sequence in Center No. 23. Among 21 patients, there were 7 (30%) patients were assigned out of sequence. Five patients were randomized within uncorrected strata.

However, the impact of these irregularity of randomization on overall antiemetic outcome in these treatment groups is expected to be minimal.

### 3.1.2 Comparison between Dolasetron and Ondansetron

Among 83 patients receiving oral ondansetron, 62 received ondansetron 8 mg x 4 doses, and 21 received ondansetron 8 mg x 3 doses. Ondansetron 8 mg x 3 doses is not effective dose. It makes the comparison between ondansetron and dolasetron in favor of dolasetron. The comparison to ondansetron tends to be biased in favor of dolasetron.

However, the sponsor stated that the elimination of the final 8 mg dose of ondansetron in the Italian centers did not confound efficacy evaluations in these patients; the timing of the fourth ondansetron dose (at 22.5 hours postchemotherapy) minimalized the impact of these missed doses. Furthermore, there was no difference in complete response rates among patients who received 8 mg x 3 doses of ondansetron (76%; 16/21 patients) compared to those who received 8 mg x 4 doses (71%; 44/62 patients).

## 3.2. Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

This reviewer performed an alternative analysis for complete response using Cochran-Mantel-Haenszel test controlling for strata for pairwise comparison among treatment groups. The results are given in Table 7.

As seen from Table 7, the results by Cochran-Mantel-Haenszel test controlling for strata are similar to those given the sponsor using logistic regression method in terms of significance.

## 3.3. Reviewer's Comments on Sponsor's Results for the Secondary

**Efficacy Variables**

This reviewer performed alternative analyses for complete-plus-major response and complete response with no nausea using Cochran-Mantel-Haenszel test controlling for strata for pairwise comparison among treatment groups. The results are given in Table 8.

As seen from Table 8, the results by Cochran-Mantel-Haenszel test controlling for strata are similar to those given the sponsor using logistic regression method in terms of significance.

3.4 **Subgroup Analysis of Complete Response**

Per the medical officer's request, this reviewer performed subgroup analyses of complete response for gender (male/female) and previous exposure to chemotherapy (naive/non-naive). The results are given in Table 9.

As seen from Table 9, for female patients, the 200 mg dose group was significantly different from the 25 mg, 50 mg, and 100 mg dose groups. For male patients, the 200 mg dose group was significantly different from the 25 mg dose group.

For non-naive patients, the 200 mg dose group was significantly different from the 25 mg and 50 mg dose groups. The 100 mg dose group was significantly different from the 50 mg dose group. For naive patients, the 200 mg dose group was significantly different from the 25 mg and 100 mg dose groups.

F. **Overall Summary and Recommendation**

**Primary Endpoint: Complete Response**

All three studies (MCPR0048, MCPR0043, and 73147-2-S-087) showed that there was a significant linear dose response trend for the "complete response" endpoint. For this endpoint, the highest observed complete response rates were achieved for the 100 mg dose in the study MCPR0048 and for the 200 mg dose in studies MCPR0043 and 73147-2-S-087.

The 731247-2-S-087 showed that the 200 mg dose was significantly more effective than each of the three lower dolasetron mesylate

doses (25 mg, 50 mg, and 100 mg). The study MCPR0048 showed that both 100 mg and 200 mg doses were significantly better than the lower doses (25 mg and 50 mg). The study MCPR0043 showed that the higher doses (50 mg, 100 mg, and 200 mg) was superior to the lower dose (25 mg).

**Secondary Endpoint: Complete Response with No Nausea**

For a more stringent efficacy measure requested by FDA, all three studies (MCPR0048, MCPR0043, and 73147-2-S-087) showed that there was a significant linear dose response trend for the "complete response with no nausea" endpoint. For this endpoint, the highest observed complete response with no nausea rate was achieved with the 200 mg dose.

The 73147-2-S-087 showed that the 200 mg dose was significantly more effective than each of the three lower dolasetron mesylate doses (25 mg, 50 mg, and 100 mg). Both studies MCPR0048 and MCPR0043 showed that both 100 mg and 200 mg doses were significantly better than the lowest doses (25 mg), but only the higher dose (200 mg) was significantly better than the 50 mg dose.

Furthermore, sponsor's sample size determination is based on establishing a linear trend in complete response with dose using a logistic regression. The sample size might be insufficient to detect the dose differences in a pairwise manner.

In the study MCPR0043, due to insufficient sample size there is not enough power to detect the difference between 100 mg and 200 mg dose groups. But, there is a numerical difference of about 10% in favor of 200 mg group in complete response, complete-plus-major response and complete response with no nausea. So, the 200 mg might be the optimal effective dose.

In conclusion, antiemetic efficacy of dolasetron mesylate tablets in prevention of CCNV was linearly related to dose. The maximal effectiveness seems to be achieved with a single dose of 200 mg.

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G. **Comments to be conveyed to the Sponsor**

The contents of Section F may be conveyed to the sponsor.

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/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 27 pages of text and 9 pages of tables.

concur: Dr. Huque /S/ 5/16/96
Dr. Smith /S/ 5/17/96

cc:
Archival NDA 20-623
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Lisook
HFD-720
HFD-720/Chron. Copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/05/15/96

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Table 1 Comparability of Treatment Groups at Baseline — Protocol MCPR0048

| | | Intent-to-Treat Population | | | | |
|---|---|---|---|---|---|---|
| Variable | Level | Dolasetron 25 mg (n=79) | Dolasetron 50 mg (n=83) | Dolasetron 100 mg (n=80) | Dolasetron 200 mg (n=78) | Between treatment p-value |
| Sex | Male | 12 (15%) | 15 (18%) | 15 (19%) | 18 (23%) | 0.6533 |
| | Female | 67 (85%) | 68 (82%) | 65 (81%) | 60 (77%) | |
| Age (mean) | | 53.1 | 54.3 | 54.5 | 54.7 | 0.9096 |
| Height (cm) (mean) | | 163.6 | 164.3 | 164.4 | 164.9 | 0.7910 |
| Weight (kg) (mean) | | 73.8 | 75.6 | 76.0 | 73.3 | 0.6285 |
| Race | Caucasian | 60 (76%) | 63 (76%) | 63 (79%) | 60 (77%) | 0.9709 |
| | Other | 19 (24%) | 20 (24%) | 17 (21%) | 18 (23%) | |
| Kamofsky status (%) | | 92.7 | 92.8 | 91.4 | 92.7 | 0.8004 |
| Site of primary neoplasm | breast | 58 (73%) | 58 (70%) | 53 (66%) | 52 (67%) | 0.7461 |
| | lung | 5 (6%) | 5 ( 6%) | 2 ( 3%) | 1 ( 1%) | (brest vs. |
| | lymphoma | 11 (14%) | 16 (19%) | 17 (21%) | 15 (19%) | all others) |
| | other | 5 ( 6%) | 4 ( 5%) | 8 (10%) | 10 (13%) | |
| Primary Chemotherapy | Doxorubicin | 31 (40%) | 37 (45%) | 32 (40%) | 35 (45%) | 0.8568 |
| | Cyclophosphamide | 47 (60%) | 46 (55%) | 48 (60%) | 43 (55%) | |
| Doxorubicin dose (mg/m2) | | 45.1 | 45.7 | 42.6 | 40.8 | 0.0032 |
| Cyclophosphamide dose | | 641.5 | 623.8 | 606.7 | 580.4 | 0.0321 |
| Duration of primary chemotherapy (min) | | 33.3 | 29.1 | 33.8 | 31.4 | 0.6001 |
| Interval between study drug and primary chemotherapy (min) | | 31.0 | 32.2 | 31.4 | 32.1 | 0.7391 |
| Previous cancer treatment | Chemotherapy | 4 ( 5%) | 3 ( 4%) | 3 ( 4%) | 1 ( 1%) | 0.6662 |
| | Radiotherapy | 9 (11%) | 6 ( 7%) | 11 (14%) | 6 ( 8%) | 0.4700 |
| | Surgery | 48 (61%) | 41 (49%) | 51 (64%) | 44 (56%) | 0.2768 |
| Concomitant use of Bensodiazepines | | 8 (10%) | 9 (11%) | 11 (14%) | 7 ( 9%) | 0.8006 |
| Concomitant use of Narcotic Analgesics | | 12 (15%) | 12 (15%) | 11 (14%) | 10 (13%) | 0.9926 |
| Concomitant use of Steroids | | 5 ( 6%) | 11 (13%) | 9 (11%) | 9 (12%) | 0.5390 |

For continuous variables, p-values are calculated from a two-way anova among the four doses controlling for investigator. For dichtomous variables, p-values are from a 3 degree of freedom chi-square test from a logistic regression model with dose as an explanatory variable.

Table 2 Reviewer's Re-analysis of Complete Response
----- Protocol MCPR0048

| Treatment | Rate | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|
| 25 mg | 24/78 (31%) | | | |
| 50 mg | 34/83 (41%) | 0.193 | | |
| 100 mg | 49/80 (61%) | <0.001 | 0.012 | |
| 200 mg | 46/78 (59%) | <0.001 | 0.027 | 0.871 |

P-values are obtained by Fisher's exact test.

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Table 3 Comparability of Treatment Groups at Baseline — Protocol MCPR0043

| | | Intent-to-Treat Population | | | | |
|---|---|---|---|---|---|---|
| Variable | Level | Dolasetron 25 mg (n=76) | Dolasetron 50 mg (n=80) | Dolasetron 100 mg (n=71) | Dolasetron 200 mg (n=80) | Between treatment p-value |
| Sex | Male | 43 (57%) | 44 (55%) | 41 (58%) | 37 (46%) | 0.4670 |
| | Female | 33 (43%) | 36 (45%) | 30 (42%) | 43 (54%) | |
| Age (mean) | | 61.6 | 59.0 | 61.7 | 62.2 | 0.4795 |
| Height (cm) (mean) | | 170.1 | 170.0 | 169.8 | 168.4 | 0.5884 |
| Weight (kg) (mean) | | 75.1 | 75.1 | 74.5 | 72.1 | 0.6219 |
| Race | Caucasian | 69 (91%) | 70 (88%) | 65 (92%) | 65 (81%) | 0.2082 |
| | Other | 7 ( 9%) | 10 (12%) | 6 ( 8%) | 15 (19%) | |
| Kamofsky status (%) | | 86.2 | 84.0 | 84.0 | 83.4 | 0.6814 |
| Site of primary neoplasm | GI | 3 ( 4%) | 6 ( 8%) | 7 (10%) | 4 ( 5%) | 0.9084 |
| | Gynecologic | 12 (16%) | 13 (16%) | 11 (16%) | 18 (23%) | (lung vs. |
| | Head/Neck | 2 ( 3%) | 4 ( 5%) | 4 ( 6%) | 1 ( 1%) | all others) |
| | Lung | 43 (57%) | 44 (55%) | 36 (51%) | 43 (54%) | |
| | Other | 16 (21%) | 13 (16%) | 13 (18%) | 14 (18%) | |
| Primary Chemotherapy | Carboplatin | 49 (65%) | 51 (64%) | 36 (51%) | 48 (60%) | 0.5051 |
| | Cisplatin | 27 (36%) | 29 (36%) | 35 (49%) | 32 (40%) | |
| Carboplatin dose (mg/m2) | | 308.1 | 310.8 | 312.1 | 313.8 | 0.9402 |
| Cisplatin dose (mg/m2) | | 34.7 | 41.4 | 31.6 | 38.8 | 0.0720 |
| Duration of primary chemotherapy (min) | | 74.4 | 72.9 | 77.9 | 76.2 | 0.8556 |
| Interval between study drug and primary chemotherapy (min) | | 32.1 | 31.9 | 30.8 | 31.5 | 0.8437 |
| Previous cancer treatment | Chemotherapy | 6 ( 8%) | 13 (16%) | 5 ( 7%) | 7 ( 9%) | 0.2174 |
| | Radiotherapy | 12 (16%) | 23 (29%) | 10 (14%) | 13 (16%) | 0.0794 |
| | Surgery | 21 (28%) | 36 (45%) | 26 (37%) | 26 (33%) | 0.1393 |
| Concomitant use of Bensodiazepines | | 6 ( 8%) | 11 (14%) | 7 (10%) | 8 (10%) | 0.6858 |
| Concomitant use of Narcotic Analgesics | | 28 (37%) | 19 (24%) | 18 (25%) | 20 (25%) | 0.2383 |
| Concomitant use of Steroids | | 4 ( 5%) | 3 ( 4%) | 11 (16%) | 4 ( 5%) | 0.0336 |

For continuous variables, p-values are calculated from a two-way anova among the four doses controlling for investigator. For dichtomous variables, p-values are from a 3 degree of freedom chi-square test from a logistic regression model with dose as an explanatory variable.

Table 4 Reviewer's Re-analysis of Complete Response
----- Protocol MCPR0043

(Intent-to-Treat Analysis)

| Treatment | Rate | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|
| 25 mg | 34/76 (45%) | | | |
| 50 mg | 57/80 (71%) | 0.001 | | |
| 100 mg | 52/71 (73%) | <0.001 | 0.856 | |
| 200 mg | 66/80 (83%) | <0.001 | 0.133 | 0.236 |

P-values are obtained by Fisher's exact test.

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Table 5 Reviewer's Re-analysis of the Secondary Efficacy ---- Protocol MCPR0043

(Intent-to-Treat Analysis)

| Efficacy Variable | Treatment | Rate | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|---|
| Complete-plus-major response | 25 mg | 42/76 (55%) | | | |
| | 50 mg | 62/80 (78%) | 0.004 | | |
| | 100 mg | 55/71 (78%) | 0.005 | 1.000 | |
| | 200 mg | 70/80 (88%) | <0.001 | 0.144 | 0.131 |
| Complete response with no nausea | 25 mg | 25/76 (33%) | | | |
| | 50 mg | 39/80 (49%) | 0.052 | | |
| | 100 mg | 44/71 (62%) | <0.001 | 0.140 | |
| | 200 mg | 56/80 (70%) | <0.001 | 0.010 | 0.307 |

P-values are obtained by Fisher's exact test.

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Table 6 Comparability of Treatment Groups at Baseline — Protocol 73147-2-S-087

| | | Intent-to-Treat Population | | | | | |
|---|---|---|---|---|---|---|---|
| Variable | Level | Ondansetron (n=83) | Dolasetron 25 mg (n=80) | Dolasetron 50 mg (n=80) | Dolasetron 100 mg (n=76) | Dolasetron 200 mg (n=80) | Between treatment p-value |
| Sex | Male | 27 (33%) | 33 (41%) | 31 (39%) | 33 (43%) | 31 (39%) | 0.6905 |
| | Female | 56 (68%) | 47 (59%) | 49 (61%) | 43 (57%) | 49 (61%) | |
| Age (mean) | | 54.3 | 53.1 | 50.9 | 53.2 | 54.2 | 0.4001 |
| Height (cm) (mean) | | 164.0 | 165.4 | 166.4 | 165.5 | 165.4 | 0.4313 |
| Weight (kg) (mean) | | 68.9 | 69.6 | 67.1 | 68.2 | 68.6 | 0.8127 |
| Karnofsky status (%) | | 92.2 | 89.8 | 92.4 | 91.8 | 90.8 | 0.6290 |
| Site of primary neoplasm | breast | 34 (41%) | 29 (36%) | 32 (40%) | 35 (46%) | 30 (38%) | 0.7617 |
| | gynecological | 6 ( 7%) | 11 (14%) | 2 ( 3%) | 4 ( 5%) | 5 ( 6%) | |
| | lung | 16 (19%) | 16 (20%) | 20 (25%) | 14 (18%) | 16 (20%) | (brest vs. |
| | lymphoma | 7 ( 8%) | 12 (15%) | 11 (14%) | 9 (12%) | 14 (18%) | all others) |
| | musculo-skeletal | 6 ( 7%) | 4 ( 5%) | 5 ( 6%) | 7 ( 9%) | 6 ( 8%) | |
| | other | 14 (17%) | 8 (10%) | 10 (13%) | 7 ( 9%) | 9 (11%) | |
| Primary Chemotherapy | Carboplatin | 17 (21%) | 21 (26%) | 14 (18%) | 12 (16%) | 18 (23%) | 0.795 |
| | Cisplatin | 5 ( 6%) | 2 ( 3%) | 2 ( 3%) | 5 ( 7%) | 4 ( 5%) | |
| | Cyclophosphamide | 25 (30%) | 22 (28%) | 25 (32%) | 19 (25%) | 22 (28%) | |
| | Doxorubicin | 20 (24%) | 19 (24%) | 15 (19%) | 17 (22%) | 21 (26%) | |
| | Other | 16 (19%) | 16 (20%) | 23 (29%) | 23 (30%) | 15 (19%) | |
| Carboplatin dose (mg/m2) | | 313.12 (n=18) | 323.8 (n=21) | 326.7 (n=15) | 320.8 (n=12) | 322.7 (n=19) | 0.8527 |
| Cisplatin dose (mg/m2) | | 21.7 (n=6) | 27.5 (n=4) | 26.1 (n=5) | 21.7 (n=6) | 32.5 (n=4) | 0.6888 |
| Cyclophosphamide dose | | 607.6 (n=46) | 628.8 (n=42) | 651.1 (n=38) | 659.8 (n=44) | 640.5 (n=41) | 0.8029 |
| Doxorubicin dose (mg/m2) | | 48.9 (n=25) | 45.4 (n=25) | 53.7 (n=20) | 43.9 (n=23) | 42.9 (n=24) | 0.3322 |
| Previous cancer treatmen | Chemotherapy | 46 (55%) | 42 (53%) | 42 (53%) | 37 (49%) | 47 (59%) | 0.7677 |
| | Radiotherapy | 19 (23%) | 14 (18%) | 9 (11%) | 15 (20%) | 21 (26%) | 0.1846 |
| Concomitant use of Bensodiazepines | | 3 ( 4%) | 0 (0%) | 2 ( 3%) | 0 (0%) | 1 ( 1%) | N/A |
| Concomitant use of Narcotic Analgesics | | 8 (10%) | 3 ( 4%) | 6 ( 8%) | 3 ( 4%) | 6 ( 8%) | 0.5157 |
| Concomitant use of Steroids | | 1 ( 1%) | 3 ( 4%) | 0 (0%) | 0 (0%) | 0 (0%) | N/A |

For continuous variables, p-values are calculated from a two-way anova among the four doses controlling for investigator. For dichtomous variables, p-values are from a 4 degree of freedom chi-square test from a logistic regression model with dose as an explanatory variable. For primary chemotherapy, p values are obtained from a chi-square test.

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Table 7 Reviewer's Re-analysis of Complete Response --- Protocol 73147-2-S-087

| Analysis | Treatment | Rate | vs. ondan p-value | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|---|---|
| ITT | Ondansetron | 60/83 (72%) | | | | |
| | Dolasetron 25 mg | 36/80 (45%) | 0.001 | | | |
| | Dolasetron 50 mg | 39/79 (49%) | 0.001 | 0.647 | | |
| | Dolasetron 100 mg | 46/76 (61%) | 0.072 | 0.053 | 0.164 | |
| | Dolasetron 200 mg | 61/80 (76%) | 0.583 | 0.001 | 0.001 | 0.039 |

P-values are obtained by Cochran-Mantel-Haenszel method for controlling strata.

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Table 8 Reviewer's Re-analysis of the Secondary Efficacy ---- Protocol 73147-2-S-087

(Intent-to-Treat Analysis)

| Efficacy Variable | Treatment | Rate | vs. ondan p-value | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|---|---|
| Complete-plus-major response | Ondansetron | 65/83 (78%) | | | | |
| | Dolasetron 25 mg | 46/80 (58%) | 0.004 | | | |
| | Dolasetron 50 mg | 47/79 (60%) | 0.004 | 0.816 | | |
| | Dolasetron 100 mg | 55/76 (72%) | 0.255 | 0.057 | 0.134 | |
| | Dolasetron 200 mg | 68/80 (85%) | 0.282 | 0.001 | 0.001 | 0.028 |
| Complete Response with No Nausea | Ondansetron | 41/83 (49%) | | | | |
| | Dolasetron 25 mg | 29/80 (36%) | 0.085 | | | |
| | Dolasetron 50 mg | 26/79 (33%) | 0.019 | 0.634 | | |
| | Dolasetron 100 mg | 37/76 (49%) | 0.788 | 0.123 | 0.064 | |
| | Dolasetron 200 mg | 51/80 (64%) | 0.066 | 0.001 | 0.001 | 0.059 |

P-values are obtained by Cochran-Mantel-Haenszel method for controlling strata.

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Table 9 Subgroup Analysis of Complete Rresponse ---- Protocol 73147-2-S-087

(Intent-to-Treat Analysis)

| Subgroup | Treatment | Rate | vs. ondan p-value | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|---|---|
| Female | Ondansetron | 39/56 (70%) | | | | |
| | Dolasetron 25 mg | 18/47 (38%) | 0.003 | | | |
| | Dolasetron 50 mg | 20/48 (42%) | 0.005 | 0.835 | | |
| | Dolasetron 100 mg | 22/43 (51%) | 0.017 | 0.289 | 0.405 | |
| | Dolasetron 200 mg | 36/49 (73%) | 0.829 | <0.001 | 0.002 | 0.032 |
| Male | Ondansetron | 21/27 (78%) | | | | |
| | Dolasetron 25 mg | 18/33 (55%) | 0.102 | | | |
| | Dolasetron 50 mg | 19/31 (61%) | 0.256 | 0.621 | | |
| | Dolasetron 100 mg | 24/33 (73%) | 0.768 | 0.200 | 0.427 | |
| | Dolasetron 200 mg | 25/31 (81%) | 1.000 | 0.035 | 0.161 | 0.560 |
| Non-naive | Ondansetron | 31/46 (67%) | | | | |
| | Dolasetron 25 mg | 21/42 (50%) | 0.129 | | | |
| | Dolasetron 50 mg | 16/41 (39%) | 0.010 | 0.379 | | |
| | Dolasetron 100 mg | 24/37 (65%) | 0.820 | 0.255 | 0.026 | |
| | Dolasetron 200 mg | 34/47 (72%) | 0.656 | 0.031 | 0.002 | 0.485 |
| Naive | Ondansetron | 29/37 (78%) | | | | |
| | Dolasetron 25 mg | 15/38 (39%) | <0.001 | | | |
| | Dolasetron 50 mg | 23/38 (61%) | 0.133 | 0.108 | | |
| | Dolasetron 100 mg | 22/39 (56%) | 0.053 | 0.173 | 0.818 | |
| | Dolasetron 200 mg | 27/33 (81%) | 0.772 | <0.001 | 0.069 | 0.025 |

P-values are obtained by Fisher's exact test.

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STATISTICAL REVIEW AND EVALUATION ---NDA

Date: MAY 20 1996

NDA # 20-623

**Applicant**: Hoechst Marion Roussel, Inc.

**Name of Drug**: Anzemet (Dolasetron mesylate) Tablet

**Indication**: Prevention of Postoperative Nausea and Vomiting

**Documents Reviewed**: NDA vol. 1.1-1.3, 1.175, 1.222-1.279, 588-591, 682 Dated September 28, 1995
PC SAS Program Corrections
Dated April 2, 1996

**Medical Reviewer**: This review has been discussed with the medical officer, Hugo Gallo-Torres, M.D., Ph.D.

A. **Background**

Dolasetron mesylate is a selective serotonin type 3 ($5\text{-}HT_3$) receptor antagonist under development by the sponsor for the prevention of nausea and vomiting due to chemotherapy and surgery.

In the current NDA, the sponsor seeks approval of oral dolasetron mesylate in two primary indications: for prevention of CCNV (cancer chemotherapy induced nausea and vomiting), and for prevention of PONV (postoperative nausea and vomiting).

This review addresses the prevention of PONV. A separate review addresses the CCNV indication.

B. **PONV Indication**

The sponsor has submitted two pivotal trial in support of the proposed claims. These two studies were placebo-controlled studies. The first study (AN-PO-0292) was conducted in Canada. The second study (73147-2-S-095) was conducted in Europe.

These two studies were designed to include only females. Females are more likely to experience postoperative emetic symptoms.

Enrollment required patients to be American Society of

Anesthesiologists (ASA) General Classification of Physical Status Class 1, 2, or 3.

Based upon results from iv dolasetron mesylate trials and the bioavailability of the oral dosage form, a dose range of 25 to 200 mg was selected for evaluation of oral dolasetron mesylate in PONV prevention.

Oral drug was administrated 1 to 2 hours prior to surgery.

Primary efficacy variable for the PONV studies was complete response as defined for the CCNV indication. Secondary efficacy variables included number of emetic episodes, time to first emetic episode or rescue medication, nausea as measured by a VAS, and complete response with no nausea. European study also included a physician's assessment of patient nausea using a four-point discrete scale.

C. **Study AN-PO-0292**

1. **Description of Study**

This was a five-arm, double-blind, placebo-controlled, randomized, multicenter trial conducted in Canada.

The objective of this study was to evaluate the dose response relationship of dolasetron mesylate 25, 50, 100, and 200 mg compared to placebo when administered as a single, oral dose 1 to 2 hours preoperatively to prevent nausea and vomiting in patients undergoing uncomplicated abdominal hysterectomy under general anesthesia.

A single oral dose of dolasetron mesylate (25, 50, 100, or 200 mg) or placebo was administered 1-2 hours before induction of anesthesia.

Female patients with ASA physical status I or II undergoing inpatient uncomplicated abdominal hysterectomy under general anesthesia participated in this trial.

The study was divided into 4 phases: screening, preoperative,

operative, and 24 hours postdose follow-up. The duration of each patient's participation was approximately 24 hours.

In case where the patient experienced more than 1 (2 or more) emetic episodes in the 24 hours following study drug administration, at the patient's request, after 5 minutes of persistent nausea, or if the investigator judged it to be necessary, standardized escape antiemetic medication could be administered.

Sample size determination was based on a linear dose response trend test on a logistic scale. The analysis plan proposed adjusting for the investigative site. The calculation postulated complete response rates of 34%, 37%, 41%, 49%, and 65% of patients in the dolasetron doses of 0, 25, 50, 100, and 200 mg, respectively. Assuming 50 patients in each dose group, for a total of 250 patients, the power for a 2-sided 0.05 significance linear trend test is 94%. In order to increase the safety database, additional patients were included for a total of 374 patients, 74 to 76 in each dose group.

2. **Sponsor's Analysis**

A total of 374 female patients were enrolled and were conducted in 13 investigators in this study. Seventy-five (75) received placebo, 76 received dolasetron mesylate 25 mg, 74 received dolasetron mesylate 50 mg, 74 received dolasetron mesylate 100 mg, and 75 received dolasetron mesylate 200 mg.

Thirteen sites were grouped into eleven pooled sites for analysis purpose by the logistic regression.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 1.

There were no statistically significant differences among the five dose groups with respect to age, height, weight, race, ASA status, history of postoperative nausea and vomiting (PONV), history of motion sickness, duration of anesthesia, and time from last free fluids to study drug administration.

## 2.2 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy endpoint was "complete response." Complete response was achieved when a patient experienced no emetic episode, received no escape medication, and was monitored for at least 23.5 hours after study drug administration.

The summary of the sponsor's analysis results for the complete response is given below.

**Protocol AN-PO-0292**
**Complete Response by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs placebo | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Placebo | 22/75 (29%) | | | | |
| Dola 25 | 27/75 (36%) | 0.3972 | | | |
| Dola 50 | 30/74 (41%) | 0.1544 | 0.5576 | | |
| Dola 100 | 40/74 (54%) | 0.0026 | 0.0267 | 0.1008 | |
| Dola 200 | 37/75 (49%) | 0.0139 | 0.1011 | 0.2909 | 0.5504 |

p=0.0015 for linear trend in dolasetron mesylate dose.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

There was a statistically significant linear trend in the proportion of complete responders across the five dose groups. The 100 mg and 200 mg doses of dolasetron mesylate were significantly more effective than placebo. The 25 mg dose group was statistically significant different from the 100 mg dose group. Efficacy achieved at the 100 mg dose was comparable to that seen at 200 mg.

## 2.3 Sponsor's Analysis of Secondary Efficacy Parameters

The secondary efficacy parameters are complete-plus-major response, time to first emetic episode or escape medication,

nausea. In addition, FDA requested analyses of complete response with no nausea.

### 2.3.1 Complete-Plus-Major Response

Major response was achieved when the patient experienced one episode, received no escape medication, and was monitored for at least 23.5 hours after study drug administration.

The summary of results of sponsor's analysis of complete-plus-major response is given below.

**Protocol AN-PO-0292**
**Complete-Plus-Major Response by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs placebo | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Placebo | 26/75 (35%) | | | | |
| Dola 25 | 37/75 (49%) | 0.0780 | | | |
| Dola 50 | 32/74 (43%) | 0.2698 | 0.5089 | | |
| Dola 100 | 43/74 (58%) | 0.0039 | 0.2436 | 0.0697 | |
| Dola 200 | 41/75 (55%) | 0.0133 | 0.4617 | 0.1642 | 0.6630 |

p=0.0063 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

The 100 mg and 200 mg doses of dolasetron mesylate were significantly different from placebo in complete-plus-major response rates.

### 2.3.2 Complete Response with No Nausea

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes, received no escape medication, was monitored for at least 23.5 hours after

initiation of the primary chemotherapy agent, and had an hour 24 VAS less than 5 mm.

The summary of results of analysis of complete response with no nausea is given below.

**Protocol AN-PO-0292**
**Complete Response with No Nausea by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs placebo | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Placebo | 11/75 (15%) | | | | |
| Dola 25 | 21/75 (28%) | 0.0510 | | | |
| Dola 50 | 21/74 (28%) | 0.0395 | 0.9000 | | |
| Dola 100 | 30/74 (41%) | 0.0005 | 0.0936 | 0.1218 | |
| Dola 200 | 27/75 (36%) | 0.0030 | 0.2679 | 0.3280 | 0.5606 |

p=0.0007 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

Comparisons of each dose to placebo of the proportion of complete responders with no nausea showed a statistically significant difference in the 50, 100, and 200 mg dose group.

## 3. Reviewer's Evaluation

### 3.1 Sponsor's Sample Size Determination

Sponsor's sample size determination is based on establishing a linear trend in complete response with dose using a logistic regression. The sample size might be insufficient to detect a low dose effect on differences between the dose groups.

### 3.2 Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

This reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 2.

As seen from Table 2, the results by Fisher's exact test are similar to those given the sponsor using logistic regression method in terms of significance.

There was a significant linear trend in complete response rates with dolasetron mesylate dose, with the highest complete response rate achieved with the 100 mg dose.

### 3.3 Reviewer's Comments on Sponsor's Results for the Secondary Efficacy

For complete-plus-major response and complete response with no nausea, this reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 3.

As seen from Table 3, the results by Fisher's exact test are similar to those given by the sponsor using logistic regression method in terms of significance.

In this study, due to insufficient sample size, there is not enough power to detect the differences among 25 mg, 50 mg, 100 mg and 200 mg groups. However, there was a significant linear trend in complete-plus-major response and complete response with no nausea rates with dolasetron mesylate dose, with the highest complete response rate achieved with the 100 mg dose.

Furthermore, in the comparison between 25 mg and 50 mg, there was a slightly difference of about 5% in favor of 50 mg group in complete-plus-major response and no differences in complete response with no nausea. But, in the comparison between 50 mg and 100 mg, there is a numerical difference of about 13% in favor of 100 mg group in complete response, complete-plus-major response, and complete response with no nausea. So the 100 mg might be the optimal effective dose.

## D. Study 73147-2-S-095

### 1. Description of Study

This was a five-arm, double-blind, placebo-controlled, randomized, multicenter trial conducted in Europe.

The objective was to evaluate the effect of single doses dolasetron mesylate in preventing postoperative nausea and vomiting in patients undergoing major gynecologic surgery.

Female patients with ASA physical status I, II or III undergoing under general anesthesia major gynecologic surgery including abdominal hysterectomy, gynecological laparotomy or vaginal hysterectomy participated in this trial.

The treatment consisted of a single dose of oral dolasetron mesylate (25, 50. 100 or 200 mg) or placebo, administered 1 to 2 hours prior to induction of anesthesia.

The primary analysis was an intent-to-treat analysis of complete response (no emetic episodes, no escape medication administrated, and patient monitored for at least 23.5 hours after study drug administration) over 24 hours using logistic regression with a test for linear trend in the proportion of complete responders with dose, controlling for investigator.

Sample size determination was based on comparing the most effective dose to placebo in the logit of the proportion of complete responders. A stepwise Dunnett's procedure was used to account for a total of 4 possible comparisons. The calculation postulated that the complete response rates in placebo and most effective dose were 45% and 65%, respectively. Assuming 150 patients in each dose group, for a total of 750 patients, the power of a 2-sided pairwise comparison with an overall 0.05 significance level of the most effective dose to placebo is 93%.

2. **Sponsor's Analysis**

A total of 793 female patients were enrolled and were conducted in 32 investigators in Europe in the study. Of the 793 patients, 156 patients received placebo, 159 patients received dolasetron mesylate 25 mg, 166 patients received dolasetron mesylate 50 mg, 154 patients received dolasetron mesylate 100 mg, and 158 patients received dolasetron mesylate 200 mg.

Four patients (all in the 200 mg dose group) did not complete the

study because their surgery was canceled after they had received study drug. These patients were not included in the intent-to-treat efficacy analysis.

Forty-two patients were considered to have major violations.

Thirty-two sites were grouped into twenty-three pooled sites to satisfy asymptotic considerations for main effects logistic regression. The following pooled sites were created: 51, 52, 54, 56, 57, and 58; 24, 34, and 55; and 35, 47, and 50.

## 2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 4.

There were no statistically significant differences among the five dose groups with respect to age, height, weight, race, ASA status, history of postoperative nausea and vomiting (PONV), history of motion sickness, and duration of anesthesia.

## 2.2 **Sponsor's Analysis of Primary Efficacy Parameter**

Complete response was achieved when a patient experienced no emetic episodes, received no escape medication, and was monitored for at least 23.5 hours after study drug administration.

The summary of results of sponsor's analysis of complete response is given below.

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**Protocol 73147-2-S-095**
**Complete Response by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs placebo | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Placebo | 55/156 (35%) | | | | |
| Dola 25 | 71/159 (45%) | 0.0722 | | | |
| Dola 50 | 95/166 (57%) | 0.0001 | 0.0243 | | |
| Dola 100 | 78/154 (51%) | 0.0062 | 0.3319 | 0.2064 | |
| Dola 200 | 73/154 (47%) | 0.0181 | 0.5491 | 0.1029 | 0.7145 |

p=0.0107 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

There was a statistically significant linear dose-response trend in the proportion of complete responders across the five dose groups.
The 50 mg, 100 mg and 200 mg doses of dolasetron mesylate were significantly more effective than placebo. The 25 mg dose group was statistically significant different from the 50 mg dose group; all other dolasetron dose group comparisons were not significant.

The 50 mg, 100 mg and 200 mg doses of dolasetron mesylate were significantly more effective than placebo, and efficacy achieved at the 50 mg dose was comparable to that seen at higher doses.

## 2.3 Sponsor's Analysis of Secondary Efficacy Parameters

The secondary efficacy parameters are complete-plus-major response, time to first emetic episode or escape medication, nausea, and FDA requested complete response with no nausea.

### 2.3.1 Complete-plus-major Response

Major response was achieved when the patient experienced one

episode, received no escape medication, and was monitored for at least 23.5 hours after study drug administration.

The summary of results of sponsor's analysis of complete-plus-major response is given below.

**Protocol 73147-2-S-095**
**Complete-plus-major Response with No Nausea by Treatment (Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs placebo | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Placebo | 66/156 (42%) | | | | |
| Dola 25 | 83/159 (52%) | 0.0653 | | | |
| Dola 50 | 101/166 (61%) | 0.0007 | 0.1149 | | |
| Dola 100 | 89/154 (58%) | 0.0058 | 0.3426 | 0.5437 | |
| Dola 200 | 85/154 (55%) | 0.0118 | 0.4763 | 0.3979 | 0.8148 |

p=0.0074 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

The 50, 100, and 200 mg dose groups were significantly different in complete-plus-major response rates from placebo.

2.3.2 **Complete Response with No Nausea**

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes, received no escape medication, was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent, and had an hour 24 VAS less than 5 mm.

The summary of results of analysis of complete response with no nausea is given below.

**Protocol 73147-2-S-095**
**Complete Response with No Nausea by Treatment**
**(Intent-to-Treat Analysis)**

| Dose (mg) | Rate | p*-value vs placebo | p*-value vs 25 mg | p*-value vs 50 mg | P*-value vs 100 mg |
|---|---|---|---|---|---|
| Placebo | 33/156 (21%) | | | | |
| Dola 25 | 48/159 (30%) | 0.0570 | | | |
| Dola 50 | 63/166 (38%) | 0.0007 | 0.1300 | | |
| Dola 100 | 53/154 (34%) | 0.0088 | 0.4553 | 0.4495 | |
| Dola 200 | 50/154 (33%) | 0.0150 | 0.5692 | 0.3544 | 0.8633 |

p=0.0117 for linear trend.
P* value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

The results from this analysis were consistent with those of complete response. Comparisons of each dose to placebo of the proportion of complete responders with no nausea showed a statistically significant difference in the 50, 100, and 200 mg dose groups, and a marginally significant difference in the 25 mg dose group.

## 3. Reviewer's Evaluation

### 3.1. Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

This reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 5.

As seen from Table 5, the results by Fisher's exact test are similar to those given the sponsor using logistic regression method in terms of significance.

There was a significant linear trend in complete response rates with dolasetron mesylate dose, with the highest complete response rate achieved with the 50 mg dose.

3.3 **Reviewer's Comments on Sponsor's Results for the Secondary**

For complete-plus-major response and complete response with no nausea, this reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 6.

As seen from Table 6, the results by Fisher's exact test are similar to those given by the sponsor using logistic regression method in terms of significance.

In this study, due to insufficient sample size there is not enough power to detect the difference among 25 mg, 50 mg, 100 mg and 200 mg groups. However, there was a significant linear trend in complete-plus-major response and complete response with no nausea rates with dolasetron mesylate dose, with the highest complete response rate achieved with the 50 mg dose.

Furthermore, in the comparison between 25 mg and 50 mg, there was a numerical difference of about 10% in favor of 50 mg group in complete response, complete-plus-major response, and complete response with no nausea. But, in the comparison between 50 mg and 100 mg, there is a slight difference of about 3% in favor of 50 mg group in complete-plus-major response and complete response with no nausea. So either the 50 mg or 100 mg might be the optimal effective dose.

E. **Overall Summary and Recommendation**

**Primary Endpoint: Complete Response**

Both studies (AN-PO-0292 and 73147-2-S-095) showed that there was a significant linear dose-response trend for the "complete response" endpoint. For this endpoint, the highest observed complete response rates were achieved for the 50 mg dose in the study 73147-2-S-095 and for the 100 mg dose in the study AN-PO-0292.

The study AN-PO-0292 showed that the 100 mg and 200 mg doses of dolasetron mesylate were significantly more effective than placebo. The 100 mg dose was statistically significant different from the 25 mg dose group.

The study 73147-2-S-095 showed that the 50 mg, 100 mg, and 200 mg doses of dolasetron mesylate were significantly more effective than placebo. The 50 mg dose was statistically significant different from the 25 mg dose group.

**Secondary Endpoint: Complete Response with No Nausea**

For a more stringent efficacy measure requested by FDA, both studies (AN-PO-0292 and 73147-2-S-095) showed that there was a significant linear dose-response trend for the "complete response with no nausea" endpoint. For this endpoint, the highest complete highest response with no nausea rate was achieved for the 100 mg dose in the study AN-PO-0292 and for the 50 mg dose in the study 73147-2-S-095.

Both studies AN-PO-0292 and 73147-2-S-095 showed that the 50 mg, 100 mg and 200 mg doses of dolasetron mesylate were significantly more effective than placebo.

In these studies, due to insufficient sample size, there is not enough power to detect the differences among 25 mg, 50 mg, 100 mg, and 200 mg groups.

In the comparison between 50 mg and 100 mg doses group, there was a numerical difference of about 13% in favor of 100 mg group in complete response, complete-plus-major response, and complete response with no nausea in the study AN-PO-0292. But, in the study 73147-2-S-095, there is a slight difference of about 3% in favor of 50 mg group in complete-plus-major response and complete response with no nausea.

Hence, the 100 mg might be the optimal effective dose which was supported by both studies (AN-PO-0292 and 73147-2-S-95).

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F. **Comments to be conveyed to the Sponsor**

The contents of Section E may be conveyed to the sponsor.

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/S/
Milton Fan, Ph.D.
Mathematical Statistician

This review consists of 15 pages of text and 6 pages of tables.

concur: Dr. Huque /S/ 5/16/96
Dr. Smith /S/ 5/17/96

cc:
Archival NDA 20-623
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Lisook
HFD-720
HFD-720/Chron. Copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/05/15/96

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Table 1 Comparability of Treatment Groups at Baseline --- Protocol AN-PO-0292

Intent-to-Treat Population

| Variable | Level | Placebo (n=75) | Dolasetron 25 mg (n=76) | Dolasetron 50 mg (n=74) | Dolasetron 100 mg (n=74) | Dolasetron 200 mg (n=75) | Between treatment p-value |
|---|---|---|---|---|---|---|---|
| Age (mean) | | 42.5 | 43.4 | 44.3 | 43.7 | 42.7 | 0.6399 |
| Height (cm) (mean) | | 162.6 | 164.5 | 164.0 | 163.2 | 162.7 | 0.2371 |
| Weight (kg) (mean) | | 67.9 | 69.5 | 71.0 | 71.8 | 71.2 | 0.5205 |
| Race | White | 64 (85%) | 61 (80%) | 63 (85%) | 59 (80%) | 59 (79%) | 0.5801 |
| | Black | 3 ( 4%) | 1 ( 1%) | 3 ( 4%) | 6 ( 8%) | 2 ( 3%) | |
| | Oriental | 7 ( 9%) | 10 (13%) | 7 (10%) | 3 ( 4%) | 12 (16%) | |
| | Other | 1 ( 1%) | 4 ( 5%) | 1 ( 1%) | 6 ( 8%) | 2 ( 3%) | |
| ASA | Status 1 | 50 (67%) | 48 (63%) | 50 (68%) | 51 (69%) | 42 (56%) | 0.4818 |
| | Status 2 | 25 (33%) | 28 (37%) | 24 (32%) | 23 (31%) | 33 (44%) | |
| History of PONV | | 40 (53%) | 32 (42%) | 38 (51%) | 32 (43%) | 33 (44%) | 0.3505 |
| History of Motion Sickness | | 17 (23%) | 22 (29%) | 25 (34%) | 18 (24%) | 21 (28%) | 0.5654 |
| Duration of Anesthesia (hrs) (mean) | | 1.47 | 1.49 | 1.48 | 1.49 | 1.53 | 0.9425 |
| Time from Last Free Fluids to Study Drug Administration (hrs) (mean) | | 8.7 | 9.1 | 9.8 | 8.4 | 8.9 | 0.1329 |

For continuous variables, p-values are calculated from a two-way anova among the five doses controlling for investigator. For discrete variables, p-values are from a 4 degree of freedom chi-square test from a logistic regression model controlling for investigator..

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Table 2 Reviewer's Re-analysis of Complete Response --- Protocol AN-PO-0292

| Analysis | Treatment | Rate | vs. placebo p-value | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|---|---|
| ITT | Placebo | 22/75 (29%) | | | | |
| | Dolasetron 25 mg | 27/75 (36%) | 0.486 | | | |
| | Dolasetron 50 mg | 30/74 (41%) | 0.172 | 0.615 | | |
| | Dolasetron 100 mg | 40/74 (54%) | 0.003 | 0.033 | 0.138 | |
| | Dolasetron 200 mg | 37/75 (49%) | 0.019 | 0.137 | 0.324 | 0.624 |
| Evaluable | Placebo | 22/68 (32%) | | | | |
| | Dolasetron 25 mg | 27/71 (38%) | 0.594 | | | |
| | Dolasetron 50 mg | 30/71 (42%) | 0.293 | 0.732 | | |
| | Dolasetron 100 mg | 36/66 (55%) | 0.014 | 0.061 | 0.173 | |
| | Dolasetron 200 mg | 36/68 (53%) | 0.024 | 0.090 | 0.236 | 0.864 |

P-values are obtained by Fisher's exact test.

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Table 3 Reviewer's Re-analysis of the Secondary Efficacy Variables --- Protocol AN-PO-0292

(Intent-to-Treat Analysis)

| Efficacy Variable | Treatment | Rate | vs. placebo p-value | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|---|---|
| Complete-plus-major response | Placebo | 26/75 (35%) | | | | |
| | Dolasetron 25 mg | 37/75 (49%) | 0.098 | | | |
| | Dolasetron 50 mg | 32/74 (43%) | 0.316 | 0.512 | | |
| | Dolasetron 100 mg | 43/74 (58%) | 0.005 | 0.326 | 0.100 | |
| | Dolasetron 200 mg | 41/75 (55%) | 0.021 | 0.624 | 0.191 | 0.742 |
| Complete response with no nausea | Placebo | 11/75 (15%) | | | | |
| | Dolasetron 25 mg | 21/75 (28%) | 0.072 | | | |
| | Dolasetron 50 mg | 21/74 (28%) | 0.048 | 1.000 | | |
| | Dolasetron 100 mg | 30/74 (41%) | <0.001 | 0.122 | 0.166 | |
| | Dolasetron 200 mg | 27/75 (36%) | 0.004 | 0.382 | 0.382 | 0.615 |

P-values are obtianed from Fisher's exact test.

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Table 4 Comparability of Treatment Groups at Baseline --- Protocol 73147-2-S-095

| | | Intent-to-Treat Population | | | | | |
|---|---|---|---|---|---|---|---|
| Variable | Level | Placebo (n=156) | Dolasetron 25 mg (n=159) | Dolasetron 50 mg (n=166) | Dolasetron 100 mg (n=154) | Dolasetron 200 mg (n=158) | Between treatment p-value |
| Age (mean) | | 43.7 | 43.3 | 42.4 | 43.4 | 42.9 | 0.4644 |
| Height (cm) (mean) | | 163.3 | 162.4 | 163.7 | 163.0 | 162.7 | 0.4663 |
| Weight (kg) (mean) | | 67.9 | 67.0 | 68.4 | 67.2 | 66.8 | 0.6350 |
| Race | White | 148 (95%) | 148 (93%) | 159 (96%) | 150 (97%) | 152 (96%) | 0.4589 |
| | Black | 7 ( 5%) | 3 ( 2%) | 0 ( 0%) | 4 ( 3%) | 1 ( 1%) | |
| | Other | 1 ( 1%) | 8 ( 5%) | 7 ( 4%) | 0 ( 0%) | 5 (3%) | |
| ASA | Status 1 | 122 (78%) | 117 (74%) | 130 (78%) | 113 (73%) | 114 (72%) | 0.5767 |
| | Status 2 | 33 (21%) | 41 (26%) | 35 (21%) | 41 (27%) | 43 (27%) | |
| | Status 3 | 1 ( 1%) | 1 ( 1%) | 1 ( 1%) | 0 ( 0%) | 1 ( 1%) | |
| History of PONV | | 51 (33%) | 48 (30%) | 51 (31%) | 46 (30%) | 61 (39%) | 0.3286 |
| History of Motion Sickness | | 28 (18%) | 35 (22%) | 24 (15%) | 24 (16%) | 35 (22%) | 0.2369 |
| Duration of Anesthesia (hrs) (mean) | | 1.59 | 1.58 | 1.62 | 1.53 | 1.54 | 0.7547 |

For continuous variables, p-values are calculated from a two-way anova among the five doses controlling for investigator. For discrete variables, p-values are from a 4 degree of freedom chi-square test from a logistic regression model controlling for investigator..

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Table 5 Reviewer's Re-analysis of Complete Response --- Protocol 73147-2-S-095

| Analysis | Treatment | Rate | vs. placebo p-value | vs. 25 mg p-value | vs. 50 mg p-value | vs. 100 mg p-value |
|---|---|---|---|---|---|---|
| ITT | Placebo | 55/156 (35%) | | | | |
| | Dolasetron 25 mg | 71/159 (45%) | 0.107 | | | |
| | Dolasetron 50 mg | 95/166 (57%) | <0.001 | 0.027 | | |
| | Dolasetron 100 mg | 78/154 (51%) | 0.008 | 0.310 | 0.262 | |
| | Dolasetron 200 mg | 73/154 (47%) | 0.038 | 0.651 | 0.093 | 0.649 |
| Evaluable | Placebo | 53/149 (36%) | | | | |
| | Dolasetron 25 mg | 69/153 (45%) | 0.101 | | | |
| | Dolasetron 50 mg | 91/157 (58%) | <0.001 | 0.031 | | |
| | Dolasetron 100 mg | 72/143 (50%) | 0.013 | 0.415 | 0.203 | |
| | Dolasetron 200 mg | 68/145 (47%) | 0.058 | 0.816 | 0.065 | 0.637 |

P-values are obtained by Fisher's exact test.

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~~Ahmad~~
Johnson



# Statistical Review - Carcinogenicity Studies


NDA: 20-623 Date: **May 14, 1996**

Applicant: Hoechst Marion Roussel INC.

Name of Drug: Dolasetron Mesylate Tablet.

Documents Reviewed: 1. Original NDA volumes 1.31 to 1.48 with date referred Dec. 4, 1995.
2. Original data submitted through CANDA by the sponsor.
3. Corrected data on a floppy diskette supplied by the sponsor on Feb. 9, 1996.

I. Background: In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. These two studies were intended to assess the carcinogenic potential of MDL 73,147 EF in mice and rats when administered orally using some selected dose levels. Dr. Tanveer Ahmad, HFD-180, who is the reviewing pharmacologist, requested the Division of Biometrics to perform the statistical review and evaluation of this study.

II. The mouse study

IIa. Design

Two separate experiments, one in male and one in female mice, were conducted over a period of 24 months. In each of these experiments there were three treated groups known as low, medium, and high, and one control group. For each sex, two hundred forty CD-1 mice were randomly divided into equal groups of 60 animals each to form the treatment groups. The dose levels for the treated groups were 75, 150, and 300 mg/kg/day for the low, medium, and high dose groups, respectively. The control groups received untreated food.

Body weight and food consumption were determined weekly for the first three months, bi-weekly for the second three months, and every four weeks thereafter. Five mice per group were killed and necropsied after 3 months of dosing. Representative tissue samples were examined for all unscheduled deaths and all mice necropsied at the termination of the study.

IIb. Sponsor's analysis

**a) Survival data analysis**

Survival data for both male and female mice were analyzed by the non-parametric log-rank test (Mantel, 1966; Cox 1972). The trend version of the log-rank test (two-sided; Tarone, 1975) and a chi-square statistic for deviation from trend were also calculated (log-dose scale).

The sponsor claimed that survival did not differ among the groups of male mice. In contrast, there were marginally significant differences in survival among the groups of female mice.

**b) Tumor data analysis**

Summary tables for a number of neoplastic lesions by organ, lesion, and sex were generated. Then, the combined prevalence and death rate method proposed by Peto et al (1980) was applied to conduct trend tests on tumor rates.

The sponsor concluded that in male mice, only the following three tumor types were found to a significant positive dose trend: Hepatocellular Adenomas ($p<0.001$) and Hepatocellular Carcinomas ($p=0.036$) as well as these two findings combined ($p< 0.001$). In female mice, only the tumor type Uterine Stromal Polyps ($p=0.04$) exhibited a significant positive dose trend.

IIc. Reviewer's analysis

This reviewer compared the intercurrent mortality rates using the survival analysis methods described by Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34, 187-220, 1972), and Gehan (A generalized Wilcoxon test for comparing arbitrarily singly censored samples, Biometrika, 52 203-223, 1965). In addition, this reviewer did the trend tests on tumor incidence rates using the method described by Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980) and the method of exact permutation trend test, developed by the Division of Biometrics. The data used in this reviewer's analysis were provided by the sponsor on a floppy diskette.

**a) Intercurrent mortality data analysis**

Table 1 shows the intercurrent mortality data of the mouse study. Figure 1a and 1b present the plots of Kaplan-Meier estimates of the survival distributions of the treatment groups for male and female mice, respectively. The homogeneity of survival distributions of four groups (Control, Low, Medium, and High ) was tested separately for male and female mice using the Cox test and

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the Generalized Wilcoxon test. The tests show that only for female mice, there is a statistically significant (at 0.05 level) linear trend ($p=0.019$ in the Cox test and $p=0.037$ in the Generalized Wilcoxon test) in the mortality. However, from Table 1, we realized that the mortality rates for the female mice at the end of two-year period study decreased from the control group to the high dose group (63.64%, 50.91%, 60%, and 38.18% for the control, low dose, medium dose, and high dose groups, respectively). Table 2A and 2B provide additional details of the p-values for the linear trend and the pairwise tests, respectively.

**b) Tumor incidence rate analysis**

*i)* Trend tests among four treatment groups

The sponsor classified the tumor types as 1) `cause of death', 2) `not cause of death', and 3) `undetermined'. Following Peto et al.(1980), the reviewer applied the `death rate method' to the first tumor type and the `prevalence' method to the second and the third tumor types to test the positive linear trend in tumor rates. For tumor types occurring in both categories (fatal and non-fatal) a combined test was performed. All tests were done using the method of exact permutation trend test. The scores used in the reviewer's analyses were 0, 75, 150, and 300 for the control, low, medium, and high dose groups, respectively. The time intervals used were 0 - 52, 53 - 78, 79-92, 93-104 weeks, interim sacrifice, and terminal sacrifice for both sexes.

The incidence rates of tumor types with p-values less than .05 are listed below.

Table 2.1(Reviewer) : Tumor types with P-value less than 0.05

| Male mice | Tumor rate | | | | |
|---|---|---|---|---|---|
| Organ/Tumor | C | L | M | H | P-value using |
| | 60 | 60 | 60 | 60 | |
| Liver/Hepatocellular Adenoma | 1 | 4 | 10 | 13 | 0.0001* |
| Liver/Hepatocellular Adenoma & Carcinoma | 8 | 11 | 25 | 26 | 0.0000* |

Multiple testing adjustment: A rule proposed by Haseman could be used to adjust the effect of multiple testings. A similar rule proposed by the Division of Biometrics, CDER/FDA was used in this review. This rule states that in order to keep the overall false-positive rate at the nominal level of approximately ten percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .025 level, otherwise the level should be set at .005.

On the basis of Division's p-value adjustment rule, the positive linear trends with P-values marked

with asterisks are considered to be statistically significant. On applying p-value adjustment rule, we notice that the tumor type Uterus Stromal Polyps in female mice is not with a significant positive trend. The observed p values are 0.04 (sponsor), 0.07 (exact test), and 0.06 (asymptotic test). Table 3 provides details of p values on the linear trend tests for the tested tumor types .

ii) pairwise comparisons of the control versus other dose groups

The following are comparisons of the incidence rates of the control groups versus those of the other dose groups (high dose, medium dose, and low dose groups) using the age adjusted Fisher exact test for tumor types whose linear trends were found to be statistically significant.

Tables 2.2, 2.3, and 2.4 provide the p values for the pairwise comparisons of the control versus high dose group, control versus medium dose group, and control versus low dose group, respectively.

Table 2.2 (Reviewer) Pairwise comparisons of Control vs. High dose groups

| Male mice | Tumor rate | | |
|---|---|---|---|
| Organ/Tumor | C | H | P-value using |
| | 60 | 60 | |
| Liver/Hepatocellular Adenoma | 1 | 13 | 0.0001* |
| Liver/Hepatocellular Adenoma & Carcinoma | 8 | 26 | 0.0000* |

Table 2.3 (Reviewer) Pairwise comparisons of Control vs. Medium dose groups

| Male mice | Tumor rate | | |
|---|---|---|---|
| Organ/Tumor | C | M | P-value using |
| | 60 | 60 | |
| Liver/Hepatocellular Adenoma | 1 | 10 | 0.0043* |
| Liver/Hepatocellular | 8 | 25 | 0.0005* |

Table 2.4 (Reviewer) Pairwise comparisons of Control vs. Low dose groups

| Male mice | Tumor rate | | |
|---|---|---|---|
| Organ/Tumor | C | L | P-value using |
| | 60 | 60 | |
| Liver/Hepatocellular Adenoma | 1 | 4 | 0.1166 |
| Liver/Hepatocellular | 8 | 11 | 0.2316 |

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For the pairwise comparisons, a rule proposed by Haseman is used to adjust the effect of multiple testings. This rule states that in order to keep the overall false-positive rate at the nominal level of approximately five percent, tumor types with a spontaneous tumor rate of no more than one percent should be tested at .05 level, otherwise the level should be set at .01. P-values marked with asterisks are considered to be statistically significant after adjusting for the effect of multiple tests.

## III. The rat study

IIIa. Design: Originally, rats were randomly assigned with stratification by weight to a control and three treated groups of 75 rats/sex. The treated groups were 75, 150, and 300 mg/kg/day for male rats and 150, 300, and 600 mg/kg/day for female rats. At approximately six months into the study an additional dose group (25 mg/kg/day in male rats and 50 mg/kg/day in female rats) was added to the study along with a matching control group (0 mg/kg/day). At the same time that the new groups were added, the highest dose group (300 mg/kg/day in male rats and 600 mg/kg/day in female rats) was removed from the study due to a high incidence of hematuria. Thus for each sex, five groups remained in the study and were split between two times of entry. In addition, based on the two times of entry, this reviewer named the five groups with dose 0, 0, 25, 75, 150 mg/kg/day for males and 0, 0, 50, 150, 300 mg/kg/day for females as old control, new control, new-low dose, old-low dose, and old-medium dose groups, respectively, for both sexes.

During the study, moribund rats were killed and necropsied. All surviving rats were killed and necropsied between 732 and 736 days. There were no interim sacrifices.

Body weight and food consumption were determined weekly for the first three months, bi-weekly for the second three months, and every four weeks thereafter. Representative tissue samples were examined for all unscheduled deaths and for rats necropsied at the termination of the study. Based on all pathology observations, cause of death or morbidity was determined for each rat when possible and tumors were classified as incidental or fatal based on this determination.

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